



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR - 2 2001

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Review of N-Butyl-1,2-benzisothiazolin-3-one Hydrolysis Studies to Support the Registration of Dolphin Fungicide, EPA File Symbol 72674-E

TO: Marshall Swindell, Product Manager, Team 33
Regulatory Management Branch I
Antimicrobials Division (7510C)

FROM: Srinivas Gowda, Chemist *Srinivas Gowda 2/21/01*
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510C)

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DP Barcode: D270035

Submission: S587122

PC Codes: 098951

EPA Reg. No.: 72674-E

Chemical Name:

N-Butyl-1,2-benzisothiazolin-3-one

Common Name: N-Butyl BIT

Data Submitter: AVECIA INC.

Empirical Formula: C₁₁H₁₃NOS

Case: 062095

Case Type: Registration

CAS#: 4299-07-4

MRID No.: 443649-02

Peer Reviewed by: Najm Shamim, RASSB

INTRODUCTION:

Avecia Inc., has submitted the hydrolysis study for N-Butyl-1,2-benzisothiazolin-3-one to meet the U.S. Environmental Protection Agency's Environmental Fate Data Requirements published in Pesticide Assessment Guidelines, Subdivision N, § 161-1 in support of registration of the proposed product, Dolphin Fungicide, EPA File Symbol number 72674-E. The submitted hydrolysis study has undergone review by Srinivas Gowda of Antimicrobials Division's Risk Assessment and Science Support Branch. The registrant used the Organization for Economic Cooperation and Development guideline (OECD 111 Hydrolysis as a Function of pH) to meet the Environmental Fate Data Requirements of the US EPA.

BACKGROUND:

The proposed product, Dolphin Fungicide, contains the active ingredient, N-Butyl-1,2-benzisothiazolin-3-one, as an antimicrobial agent (to control fungi and bacteria) for the preservation of plastics.

The Hydrolysis study entitled "Abiotic Degradation: Hydrolysis as a Function of pH as required by EPA Guideline 161-1" by T.M. Williams, Zeneca specialties, Analytical Sciences Group (ASG), Specialties Research Centre, Hexagon House, Blackley, Manchester M9 8ZS, Project 504624 dated April 1996 has been submitted to the Agency (MRID number 443649-02) to fulfill the requirements for the registration of the product, Dolphin Fungicide, EPA File Symbol No. 72674-E. The environmental fate data are submitted in accordance with the testing guidelines of OECD Guidelines 111 (Hydrolysis as a Function of pH).

METHODOLOGY:

The hydrolysis study was conducted according to the method, "Methods for the Determination of Physico-Chemical Properties. Official Journal of the European Communities L383A, Vol. 35, 29th December 1992."

The method employed, "Degradation-Abiotic Degradation Hydrolysis as a Function of pH" is based on the OECD Test Guideline, "OECD, Paris, 1981, Test Guideline 111, Decision of the Council C(81) 30 final."

The Study Report provided a very brief description of the method. Hydrolysis of the test substance was studied at pHs 4, 7, and 9. The solutions of test substance were prepared in pH buffered solutions and stored in an oven at 50°C. As the test substance has no appreciable aqueous solubility (<0.0005 g/L), methanol was added so that the solutions contained 1 percent (v/v) of methanol. At different time intervals, small aliquots of samples were taken from the solutions and analyzed for N-n-butyl-1,2-benzisothiazolin-3-one using high performance liquid chromatography (HPLC). Hydrolysis was monitored for a total of 6 days.

Apparatus

The HPLC instrument model HP1090M was used to analyze the test substance. However, detailed information on instruments and devices used in the study was not provided.

Test Substances and Reagents

Five samples from individual lots of test substances and a blend of all the five samples were used in the overall study. However, only the blend sample was used in the hydrolysis study. The test substance was manufactured at Huddersfield Works, ZENECA Fine Chemicals Manufacturing Organization. The blend sample was found to contain 95.5 percent of N-n-butyl-1,2-benzisothiazolin-3-one. The composition of the blend sample is provided in Table 1.

The pH buffer solutions were prepared as follows:

- pH 4 Buffer Solution – 164 ml of 0.2 M glacial acetic acid with 36 ml of 0.2 M sodium acetate was diluted to 1 liter with distilled water;
- pH 7 Buffer Solution – 296 ml of 0.1 M sodium hydroxide with 500 ml of 0.1 M mono-potassium phosphate was diluted to 1 liter with distilled water;
- pH 9 Buffer Solution – 213 ml of 0.1 M sodium hydroxide with 500 ml of 0.1 M boric acid was diluted to 1 liter with distilled water.

Table 1. Composition of the Test Substance (Blend Sample)

Components	Contents
Water Content	< 0.1 percent (w/w)
Sulfated Ash	<0.1 percent (w/w)
The main component – N-n-butyl-1,2-benzisothiazolin-3-one	95.5 percent (w/w)
The major impurity – N-ButylBisamide	4.8 percent (w/w)
Other organic impurities	1.3 percent (w/w)
Organic Purity	99.8 percent (w/w)

Calibration, Standardization, and Operating Conditions of HPLC

HPLC was used to determine the test substance in this study. However, the procedures and standards used for calibration were not provided in the Study Report. The operating conditions of HPLC were provided and re-summarized in Table 2.

Table 2. HPLC Operating Conditions

Instrument:	HP1090M		
Column:	25cm × 0.32 cm Spherisorb S5 ODS-1		
Column Oven:	40°C		
Mobile Phase:	Eluent A: Distilled Water: Acetonitrile: Methanol: Glacial Acetic Acid = 60:25:20:2.5 Eluent B: Acetonitrile: Methanol: Glacial Acetic Acid = 54:45:2.5		
Gradient Profile:	Time (minutes)	% A	%B
	0.00	100	0
	12.00	25	75
	15.00	25	75
	16.00	100	0
	21.00	100	0
Detective Wavelength:	254 nm		
Injection Volume:	10 µl		
Flow rate	0.75 ml/minute		

Procedure

The hydrolysis study was conducted according to the following procedures:

1. Two stock solutions (25 ml each) of test substance were prepared using methanol;
2. Duplicate test solutions (TEST A and TEST B) were prepared by dilution of 1.0 ml of each stock solution to 100.0 ml with the appropriate buffer solutions;
3. Test solutions were placed in an oven at 50°C after taking small aliquots for initial analysis;
4. Small aliquots of solutions were taken at intervals of 0.875, 1.875, 4.875, and 6 days;
5. Samples were analyzed for the main component of the test substance – N-n-Butyl-1,2-Benzisothiazolin-3-one, using HPLC.

SUMMARY OF DATA:

The hydrolysis study results are provided in the Study Report and re-summarized in Table 3 of this review report. No significant hydrolysis of the test substance was detected at pH 4 and 7 after maintaining test solutions in an oven at 50°C for 6 days. However, 4 to 5 percent of loss of the test substance due to hydrolysis was observed at pH 9. Since the percent loss of the test substance was less than 10 percent, the half-life of hydrolysis was not calculated. According to the Study Report, the less than 10 percent loss of the test substance in 5 days was estimated to be equivalent to a half-life of more than one year at a more representative field temperature of 25°C. However, the study did not provide the procedure for converting ~10 percent loss of the test chemical at 50°C to a half-life of more than 1 year at 25°C.

Table 3. Data Summary on Hydrolysis of N-n-Butyl-1,2-Benzisothiazolin-3-one

Time (days)	TEST 1		TEST 2	
	Concentrations (g/L)	Percent of Loss (%)	Concentrations (g/L)	Percent of Loss (%)
pH 4 at 50°C				
0	0.0288	— ^a	0.0281	—
0.875	0.0293	—	0.0282	—
1.875	0.0292	—	0.0284	—
4.875	0.0299	—	0.0289	—
6	0.0297	—	0.0288	—
pH 7 at 50°C				
0	0.0291	—	0.0282	—
0.875	0.0293	—	0.0283	—
1.875	0.0292	—	0.0284	—
4.875	0.0296	—	0.0290	—
6	0.0294	—	0.0286	—
pH 9 at 50°C				
0	0.0295	—	0.0287	—
0.875	0.0290	2	0.0282	2 (Test 1 & 2)
1.875	0.0288	2	0.0281	2 (Test 1 & 2)
4.875	0.0283	4	0.0282	4 (Test 1) 2 (Test 2)
6	0.0281	5	0.0277	5 (Test 1) 4 (Test 2)

a — No loss was detected in solutions at pH 4 and pH 7.

RASSB's CONCLUSIONS AND RECOMMENDATIONS:

Risk Assessment and Science Support Branch (RASSB) concludes that the submitted hydrolysis study does not satisfy the requirements for a hydrolysis study in water because the registrant employed the guideline 111 (Hydrolysis as a Function of pH) published by the Organization for Economic Cooperation and Development (OECD) instead of the required US Environmental Protection Agency's Pesticide Assessment Guidelines, Subdivision N, § 161-1. However, the study does provide supplemental information suggesting that Dolphin Fungicide does not appreciably hydrolyze over a thirty day period. Therefore, RASSB recommends that the hydrolysis studies on N-Butyl-1,2-benzisothiazolin-3-one be classified as supplemental and used to support the registration.

cc: Srinivas Gowda/RASSB/AD

Chemical (098951)/AD

Reviewed by: Srinivas Gowda, Microbiologist/Chemist, Team 1 Srinivas Gowda, Date 2/21/01

Secondary Reviewer: Najm Shamim, Ph.D., Chemist, Team 2 Ans, Date 2/21/2001

DATA EVALUATION RECORD

STUDY TYPE: Hydrolysis

DP BARCODE: D270035

PC CODE: 098951

SUBMISSION CODE: S587122

CASE TYPE: Registration

TEST MATERIAL: N-Butyl-1,2-benzisothiazolin-3-one

CITATION: "Abiotic Degradation: Hydrolysis as a Function of pH as required by EPA Guideline 161-1" by T.M. Williams, Zeneca specialties, Analytical Sciences Group (ASG), Specialties Research Centre, Hexagon House, Blackley, Manchester M9 8ZS, Project 504624 dated April 1996 has been submitted to the Agency (MRID number 443649-02) to fulfill the requirements for the registration of the product, Dolphin Fungicide, EPA File Symbol No. 72674-E.

SPONSOR: Avecia Inc.